RESEARCH LETTER

Evaluation of Results 1 Year Following Short-term Use of Ranibizumab for Vitreous Hemorrhage Due to Proliferative Diabetic Retinopathy

Vitreous hemorrhage from proliferative diabetic retinopathy can cause vision loss and preclude panretinal photocoagulation (PRP). The Diabetic Retinopathy Clinical Research Network (DRCR.net) investigated whether intravitreal ranibizumab compared with intravitreal saline had a beneficial effect on the vitrectomy rates of eyes with vitreous hemorrhage from proliferative diabetic retinopathy precluding complete PRP. Eyes were randomly assigned to 0.5 mg of ranibizumab (n = 125) or saline (n = 136), which was injected into the vitreous at baseline, 4 weeks, and 8 weeks. The primary end point was assessed at 16 weeks; for safety purposes, participants were followed for 52 weeks. After 16 weeks, each participant’s management was at the investigators’ discretion.

As previously reported, by the 16-week end point, the cumulative probability of vitrectomy was 12% for eyes assigned to ranibizumab compared with 17% for saline (difference, 4%; 95% CI, −4% to 13%), suggesting little likelihood of a clinically important difference. The study did not address whether ranibizumab or saline injections were superior to observation alone. Previously reported secondary outcomes suggested a short-term positive biological effect of ranibizumab compared with saline: (1) the ability to complete PRP without vitrectomy by 16 weeks was 44% for the ranibizumab group vs 31% for the saline group (P = .05); (2) the mean (SD) visual acuity improvement from baseline to 12 weeks was 22 (23) letters with ranibizumab vs 31% for the saline group (difference, 5%; 95% CI, −7% to 17%; P = .04); (3) recurrent vitreous hemorrhage within 16 weeks occurred in 6% of eyes with ranibizumab compared with 17% of eyes with saline (P = .01). No short-term safety concerns were noted. Herein, we present the 1-year follow-up results to the original study.

Results | Overall, 82% of the participants completed a 52-week visit, 2% died, and 16% were lost to follow-up. The 1-year cumulative probability of vitrectomy was 35% for the ranibizumab group vs 41% for the saline group (difference, 5%; 95% CI, −7% to 17%; P = .35) (Figure 1). The combined 1-year cumulative probability of vitrectomy in both groups was 38% (95% CI, 32% to 44%). The cumulative probability of complete PRP by the 52-week visit was 55% for the ranibizumab group vs 42% for the saline group (P = .04) (Figure 2). The mean (SD) visual acuity letter score at 52 weeks was 65 (22) (approximate Snellen equivalent, 20/50 ± 4.4 lines) in the ranibizumab group vs 64 (26) (approximate Snellen equivalent, 20/50 ± 5.2 lines) in the saline group (P = .83). Between 16 and 52 weeks of follow-up, 17 eyes in the ranibizumab group received 34 anti-vascular endothelial growth factor injections and 31 eyes in the saline group received 46 anti-vascular endothelial growth factor injections. Following the 16-week end point, investigator-reported recurrent vitreous hemorrhage appeared similar between treatment groups (13 of 102 eyes in the ranibizumab group and 15 of 113 eyes in the saline group). After 16 weeks, traction and/or rhegmatogenous retinal detachments on clinical examination or ultrasoundography were seen in 7 eyes in the ranibizumab group compared with 11 eyes in the saline group. Three participants in the ranibizumab group (2%) and 8 participants in the saline group (6%) had an Antiplatelet Trialists’ Collaboration-defined systemic adverse event (P = .22).

Figure 1. Cumulative Probability of Vitrectomy Surgery by 52 Weeks of Study Follow-up

<table>
<thead>
<tr>
<th>Follow-up, wk</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>125</td>
<td>124</td>
<td>120</td>
<td>114</td>
<td>107</td>
<td>78</td>
</tr>
<tr>
<td>Saline</td>
<td>136</td>
<td>133</td>
<td>130</td>
<td>126</td>
<td>111</td>
<td>78</td>
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<tr>
<td>Events, No.</td>
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<td>5</td>
<td>7</td>
<td>28</td>
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<td>Eyes at risk, No.</td>
<td>78</td>
<td>NA</td>
<td></td>
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<td>Events, No.</td>
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<td>1</td>
<td>4</td>
<td>15</td>
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<td>78</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Categorization of events and censoring into intervals were defined by the visit date if the visit occurred; otherwise, they were defined using the target date of the visit. The number of eyes at risk indicates those with follow-up data at the start of the interval and no vitrectomy prior to the start of the interval; the number of events indicates the number of eyes with vitrectomy during the subsequent 4-week period. No follow-up was performed between 16 and 52 weeks. NA indicates not applicable.
Discussion | More than one-third of eyes enrolled in the study underwent vitrectomy in both groups by 1 year. The ability to perform PRP occurred more frequently in the ranibizumab group; however, the greater improvement in mean visual acuity observed at 12 weeks was not present at 52 weeks. By the 52-week visit, there were no apparent differences on safety outcomes between the 2 interventions.

The evaluation of intravitreal saline vs ranibizumab given at baseline, 4 weeks, and 8 weeks after randomization in eyes with vitreous hemorrhage showed no difference in safety between the 2 treatment groups at 52 weeks. The absence of any clinically relevant differences in rates of vitrectomy noted through the primary end point at 16 weeks persisted through the 52-week safety follow-up.

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Author Contributions: Mr Glassman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bhavsar, Glassman, Jampol, Kinyoun. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: Bhavsar, Jampol, Kinyoun. Statistical analysis: Torres, Glassman. Obtained funding: Glassman. Administrative, technical, or material support: Glassman, Jampol. Study supervision: Bhavsar, Glassman, Jampol, Kinyoun.

Conflict of Interest Disclosures: Dr Bhavsar has served as a consultant for Allergan. Dr Jampol has served as a consultant for Quintiles/Stem Cell Organization. A complete list of all DRCR.net investigator financial disclosures is available at http://www.drcr.net. No other disclosures were reported.

Funding/Support: This work was supported through cooperative agreements EY1423, EYO18817, and EYO22307 from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, US Department of Health and Human Services. Genentech provided the ranibizumab study drug for this trial and funds to the DRCR.net to defray the study's clinical site costs.

Role of the Sponsor: The National Institutes of Health participated in oversight of the conduct of the study and review of the manuscript but not directly in the design or conduct of the study, collection, management, analysis, and interpretation of the data, or preparation of the manuscript. Genentech had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Trial Registration: clinicaltrials.gov Identifier: NCT00996437

Group Members: A complete list of the DRCR.net investigators was published in JAMA Ophthalmol. 2013;131(3):283-293.

Disclaimer: Neil M. Bressler, MD is the JAMA Ophthalmology Editor in Chief but was not involved in the review process or the acceptance of the manuscript.

Additional Information: As described in the DRCR.net Industry Collaboration Guidelines (http://www.drcr.net), the DRCR.net had complete control over the design of the protocol, ownership of the data, and all editorial content of presentations and publications related to the protocol.

Additional Contributions: Neil M. Bressler, MD, Wilmer Eye Institute, Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, Maryland, made substantial contributions to this article, including conception and design, analysis and interpretation of the data, and critical revision for important intellectual content; he received a grant from the National Institutes of Health as principal investigator of the Operations Center for work on this project.
